PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220 C2948-PCT

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/BE2004/000118	16.08.2004	14.08.2003

International Patent Classification (IPC) or both national classification and IPC
A61P07/02, A61K39/395, C07K16/36

Applicant
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1. This opinion contains indications relating to the following items:

response: 14.8.03 + 22m = 14.6.0.
02.2.05 + 3m = 02.5.0

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/BE2004/000118

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed.

   ☒ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☐ The following document has not been furnished:

   ☐ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. ☒ It has not been possible to consider the validity of the priority claim because a copy of the priority document was not available to the ISA at the time that the search was conducted (Rule 17.1). This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

4. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 15-19 (as to IA) and 15 (partially)

because:

☒ the said international application, or the said claims Nos. 15-19 (as to IA) relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 15 (partially)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-25
	No:	Claims	26,30,31
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-33
Industrial applicability (IA)	Yes:	Claims	1-14,20-33
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.
PCT/BE2004/000118

Reference is made to the following documents:

D1: Wright A. et al. (1991)
D2: Kato M et al. (1993)
D3: Sato K et al. (1996)
D4: Khurana S et al. (1997)
D5: WO0104269 (cited by the applicant in the description)
D6: Singh I et al. (2002)
D7: Kallas A et al. (2002)
D8: Blood (2003)102(11):163a

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1 **Rule 67.1(iv) PCT**

1.1 Claims 15-19 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

2 **Art. 5 and 6 PCT**

2.1 Claim 15 relates to an extremely large number of possible methods. Support within the meaning of Art. 6 PCT and/or disclosure within the meaning of Art. 5 PCT is to be found, however, for only a very small proportion of the methods claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search and examination over the whole of the claimed scope is impossible. Consequently, the search and examination has been carried out for those parts of the claim which appear to be supported and disclosed, namely those parts relating to the method for treatment comprising administering the antibody Krix-1 identified by seq.ID 1-4 (DNA and amino acid sequence of the heavy and light chain; see pg.13 and pg. 58 l.19-23 of the application), modified either by deglycosylation with N-glycosydase or by mutations at specific positions e.g. 49 (Thr to Ala) or at position 47 (Asn to Gln) (see ex. 7) or by production in CHO cell line, to treat thromboembolic disorders (see ex.4-6,9).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 **Art.5 and 6 PCT**

1.1 The subject-matter of claim 1 lacks support, essential technical features, clarity and disclosure (Art. 5 and 6 PCT) the reason being the following:

1.2 D1 studies the effect of modifying the glycosylation of the variable region of an antibody binding to dextran (see abstract). This study clearly shows that changes in the position of the carbohydrate in the variable regions affect antigen binding in different ways, ranging from inhibitory to increased binding. Moreover the structure of the carbohydrate varied depending on the position in the variable region; and the amino acid substitution required to introduce the glycosylation consensus motif has also an impact on the affinity for the antigen (see pg.2717 right-hand column l.25-31; pg.2720 right-hand column l.1-6; pg.2721 left-hand column l.14-17; tab.II).

1.3 D2-D4 disclose specific monoclonal antibody, glycosylated in the variable region, wherein modifying the glycosylation has completely different results. The antibody disclosed in D2 shows an improved binding to the specific antigen after deglycosylation (see abstract); whereas in D3, deglycosylation of the antibody has no impact on the binding properties (see abstract). But in D4, deglycosylation of the antibody reduces the binding properties (see pg.467 left-hand column 2nd paragraph).

1.4 On the basis of D1-D4 it is obvious that modifications in the glycosylation of the variable region of antibodies have different effects which are strictly antibody dependent.

1.5 Therefore claim 1 is not supported by the description as required by Art.6 PCT, as its scope is broader than justified by the description and examples. The claim refers to "inhibitory antibody", "against Factor VIII" wherein "the glycosylation of its variable region has been modified" and "has the same affinity compared to the native antibody". However, the application exemplifies only the production of specific modified anti-Factor VIII monoclonal antibody having these characteristics. In the light of the prior art (D1-D4)

it appears unlikely that modification of a different inhibitory antibody would lead to the same result. Consequently no generalization is envisaged for reference to **generic** inhibitory antibodies against Factor VIII.

1.6 Moreover claim 1 does not meet the requirements of Art.6 PCT in that the matter for which protection is sought is not clearly defined. In a first aspect the subject-matter of present claim lacks the effect of the modification of the antibody, namely that glycosylation is modified in order to modify the inhibitory activity (see pg.5 l.14-18 of the application). In a second aspect, the claim attempts to define the subject-matter in terms of the result to be achieved, namely "modification of the variable region" and "same affinity compared to the native antibody". However this result is linked to a specific antibody and to specific modification namely: monoclonal antibody Krix-1 identified by seq.ID 1-4 (DNA and amino acid sequence of the heavy and light chain; see pg.13 and pg. 58 l.19-23 of the application), modified either by deglycosylation with N-glycosydase or by mutations at specific positions e.g. 49 (Thr to Ala) or at position 47 (Asn to Gln) (see ex. 7) or by production in CHO cell line.

1.7 These features are essential technical features to the definition of the invention. Since independent claim 1 does not contain these features it does not meet the requirement following from Art.6 PCT taken in combination with Rule 6.3(b) PCT that any independent claim must contain all the technical features essential to the definition of the invention.

1.8 Since the application as such does not provide the means on how to produce generic modified inhibitory anti-Factor VIII according to claim 1, the claim also lacks disclosure (Art.5 PCT) over its whole scope.

1.9 The same objections cited for claim 1 are valid, mutatis mutandis, for claims 20 (and related product claim 24), 25,26(and related product claim 30-32) and 33 of the application, referring to generic Factor VIII inhibitory antibodies.

2 **Novelty** (Art.33(2) PCT) and **Inventive Step** (Art.33(3) PCT)

2.1 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 1 is novel (Art.33(2) PCT), but does not involve an inventive step in the sense of Art. 33(3) PCT.

2.1.1 The above-mentioned lack of support, essential technical features, clarity and disclosure notwithstanding, an attempt has been done to asses novelty and inventive step for the subject-matter of claim 1.

2.1.2 D5 is regarded as being the closest prior art to the subject-matter of present claim and discloses the production of an inhibitory anti-Factor VIII antibody Krix-1, characterised by heavy and light chains having 100% and >99% amino acid and DNA identity with the heavy and light chain of the antibody disclosed in the application (see ex.5 and fig.8 and 9). Fab fragments of this antibody are produced, which however show lower binding affinity to the antigen compared to Krix-1 (see pg. 25 l.4-pg.26 l.8). The applicant is the first to produce an inhibitory antibody binding to Factor VIII, characterized in that the glycosylation of its variable region has been modified, but the affinity is the same of the native antibody. The subject-matter of claim 1 is therefore new in the light of the available prior art (Art.33(2) PCT).

2.1.3 However, in order to establish an inventive step, all the technical features necessary to solve the problem posed by the application should be present in the subject-matter of claim 1. Since this is not the case, present claim does not meet the requirements of Art.33(3) PCT.

2.2 **The foregoing objections under Art. 5, 6 and 33(3) PCT cited for the subject-matter of claim 1 affect, mutatis mutandis, the subject-matter encompassed by related products and methods claims 13,14-18. Therefore:**

2.2.1 The subject-matter of claims 13,14-18 is new (Art.33(2) PCT), but not inventive (Art.33(3) PCT), the reason being the same, mutatis mutandis, as for claim 1 (see point 2.1.3). Furthermore the products and methods referred to in present claims appear to be either standard products in this technical field (claim 14) or obvious in the light of the prior art. D6 shows the antithrombotic efficacy of LE2E9, an anti-factor VIII partially inhibitor antibody, in a mouse model for venous thrombosis (see the whole doc). An inventive step for claims 15-18 may be acknowledge only if the antibody (according to claim 1) used in the method is inventive.

2.3 The same is valid for the subject-matter of claims 20 (and related product claim 24), 25,32 and 33 which is new (Art.33(2) PCT), but not inventive (Art.33(3) PCT), which do not encompass all the essential technical features for the definition of the invention,

therefore do not solve the problem of the application and do not fulfill the requirements of Art.33(3) PCT.

2.4 The subject-matter of claim 26,30 and 31 is not new (Art.3(2) PCT).

2.4.1 D7 studies competitive binding between an anti-Factor VIII inhibitory antibodies LE2E9, binding to the C1 domain, BO2C11 and patients antibody (inhibiting FVIII activity) (see pg.295, right-hand column, 2nd paragraph). D6 is detrimental to the novelty of the subject-matter of claims 26,30 and 31.

2.4.2 D5 discloses the production of an inhibitory anti-Factor VIII antibody Krix-1, characterised by heavy and light chains having 100% and >99% amino acid and DNA identity with the heavy and light chain of the antibody disclosed in the application (see ex.5 and fig.8 and 9). This antibody is effective in inhibiting venous thrombosis in an hamster model (ex.7). D5 anticipate the subject-matter of claim 30 and 31 which is therefore not novel (Art.33(2) PCT.

2.5 Dependent claims 2-12,19,21-23,28-29 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step, since they do not appear to lead to any surprising effects or advantages.

2.6 For the assessment of the present claims 15-19 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VI

Certain documents cited

Certain published documents

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*

Should the priority date of the present priority turn out not to be valid, then document "Blood (2003)102(11):163a" would become relevant in the context of novelty and inventive step

Re Item VII

Certain defects in the international application

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1-D4 and D6,D7 are not mentioned in the description, nor are these documents identified therein.

Re Item VIII

Certain observations on the international application

1 Claims 9-12 are not supported by the description as required by Art.6 PCT. Present claims recite "at least 70% sequence similarity". Support however can only be found for antibodies comprising the specific sequence with a mutation to remove the glycosylation consensus site (see also point 1.2.2). The scope of the claims is therefore broader than justified by the description and examples.

2 Claim 25 does not meet the requirement following from Article 6 PCT taken in combination with Rule 6.3(b) PCT that any independent claim must contain all the technical features essential to the definition of the invention. It is clear from the description e.g. on pg.4 l.23-27 that the following feature is essential to the definition of the invention: "producing and inhibitory antibody ... inhibiting FVIII between 20 and 85% and **with substantially the same affinity"**. Since independent claim 25 does not contain this feature it does not meet the requirement following from Article 6 PCT taken in combination with Rule 6.3(b) PCT that any independent claim must contain all the technical features essential to the definition of the invention.

3 Claim 33 is not supported by the description as required by Art. 6 PCT, as its scope is

broader than justified by the examples. Present claim refers to a method for obtaining a library of at least two inhibitory antibodies against factor VIII ..... "with substantially the same affinity" and "comprising modifying the glycosylation in the variable region **and/or by generating an antibody fragment**"..... Support in the application can however only be found for modification concerning the glycosylation in the variable region. Example 11 of the application shows the production and inhibition properties of scFv from Krix-1 (and the deglycosylated derivative Krix-1Q) However, the affinity of said scFv has not been tested. From D5 (see pg. 25 l.4-pg.26 l.8) it appears that Fab fragments of Krix-1 have reduced affinity compared to the whole antibody and casts doubt on the reproducibility of the method according to claim 33. Consequently, since the application as a whole does not provide the means in order to carry out present method **by generating an antibody fragment** the claim also lacks disclosure (Art.5 PCT).

4 The term "fragment" (claims 1-13,16-18,20,21,25) and "derivative" (claim 32) are vague and unclear and leave the reader in doubt as to the meaning of the technical features to which it refers, thereby rendering the definition of the subject-matter of said claims unclear, Art.6 PCT.

5 The expressions Krix-1, Krix-1Q and Krix-1A (in claims 5,7,19,23,27,30,32) are internal designations for monoclonal antibodies which in themselves convey no technical information for the skilled person. Thus, these expressions are unclear in the sense of Art.6 PCT.

6 Although claims 20 and 33 have been drafted as separate independent claims, they appear to relate effectively to the same subject-matter and to differ from each other only with regard to subject-matter which lacks support under Art.6 PCT and disclosure under Art. 5 PCT (see also the remarks under point). The aforementioned claims therefore lack conciseness and as such do not meet the requirements of Article 6 PCT.